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THE NORMAL AND EPILEPTIC THALAMUS: DEVELOPMENTAL EXPRESSION OF HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED (HCN) CHANNEL ISOFORMS AND THEIR ROLE IN EPILEPTOGENESIS

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Rationale: (I_h), the current carried by the HCN channels, contributes to neuronal membrane properties and network integration. Thalamic HCN channels participate in thalamocortical oscillations that are involved in sleep and have been implicated in absence epilepsies (Di Pasquale et al., 1997; Strauss et al., 2004; Budde et al., 2005). In both thalamus (absence) and hippocampus (febrile seizure-related limbic epilepsy), the epilepsies associated with HCN channel dysfunction commence during development. This suggests that disrupted developmental regulation of thalamic HCN channel expression may contribute to the process of initiation of these epilepsies. Therefore, we studied the developmental expression patterns of HCN channels in thalamus, and probed the role of these channels in an established model of absence epilepsy, the Genetic Absence Epilepsy Rat from Strasbourg (GAERS).

Methods: We used *in situ* hybridization (quantitative and single-cell resolution) to investigate the thalamic expression of HCN channel isoforms 1, 2 and 4 in Sprague-Dawley rats at postnatal days (P) 2, 7, 11, 18 and 60, as well as in adult GAERS rats and age/strain matched controls. The developmental studies were augmented by immunocytochemistry.

Results: (1) HCN1, 2 and 4 isoforms were expressed in distinct patterns in thalamus as early as P2. The HCN1 isoform resided primarily in thalamic nuclei that inter-connect with limbic regions (e.g., anterodorsal, lateral posterior). In contrast, HCN2 channels were robustly expressed in nuclei of the ventral group that relay somatosensory input to cortex (e.g., ventral posteromedial; VPm). HCN2, but not HCN4, was found in reticular nucleus (Rtn). In general, expression patterns in immature thalamus were similar to those in adults. (2) Levels of HCN2 and 4 isoforms did not distinguish GAERS rats from controls. However, HCN1 mRNA levels were strongly increased in the VPm (58%) and Rtn (28%). (3) Consistent with the increased contribution of HCN1 to the molecular make-up of thalamic I_h in the GAERS, the h-current in these rats was much less sensitive to non-saturating levels of cAMP, influencing thalamocortical oscillations (Kuisle et al., 2006).

Conclusions: (1) Nucleus-specific expression patterns of thalamic HCN isoforms are established early postnatally, consistent with a key role for these channels in fundamental functions of the thalamocortical network (2) Increased expression of HCN1 channels in GAERS rats is associated with I_h dysfunction that may contribute to their epileptic phenotype. (Supported by NIH NS 47993 (ALB); NS 35439 (TZB).)